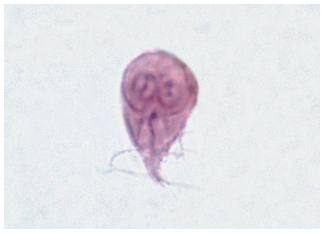

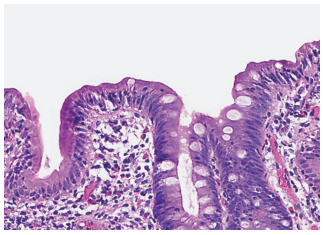

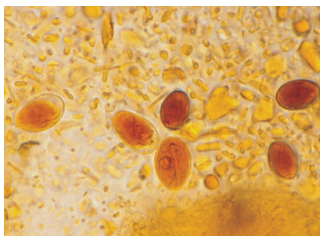

6

Giardiasis

Ellen M. Andersen, Mary K. Klassen-Fischer, and Ronald C. Neafie

Introduction

Definition

Giardiasis is gastroenteritis caused by the flagellate protozoon *Giardia intestinalis* (syn. *Giardia lamblia*) of the order Diplomonadida, family Hexamitidae.

Synonyms

Synonyms for *G. intestinalis* include *Giardia duodenalis, Giardia lamblia, Giardia enterica, Lamblia intestinalis, Cercomonas intestinalis,* and *Megastoma enterica*. The name *G. duodenalis* is sometimes followed by the name of the animal from which the parasite was obtained. Lambliasis and lambliosis are also synonyms for giardiasis.

General Considerations

Until the early 1940s, *G. intestinalis* (syn. G. *lamblia*) was considered a harmless commensal. It is now recognized as a major cause of waterborne enteric disease throughout tropical and temperate regions. In 1682 Leeuwenhoek briefly described an organism that was probably *G. intestinalis*. In 1859 Lambl gave the first comprehensive description of the trophozoite stage, followed by Grassi's description of the cyst stage in 1879. In 1915 Stiles established the name *Giardia lamblia* in honor of Giard, a French biologist and parasitologist (1846-1908), and Lambl.

Epidemiology and Transmission

Giardiasis is cosmopolitan, but infection rates vary regionally from 1% to more than 25%. Rates are higher in warmer climates and in crowded unsanitary environments. Men and women are affected equally, but age is a risk factor. Children under age 5 years are 3 times more susceptible to infection than adults, and prevalence of cyst passage in

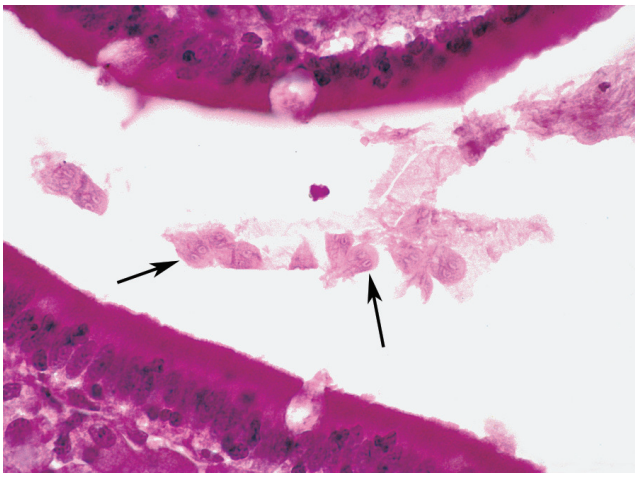

Figure 6.1
Multiple piriform *Giardia intestinalis* trophozoites (arrows) in lumen of duodenum demonstrating paired nuclei. x400

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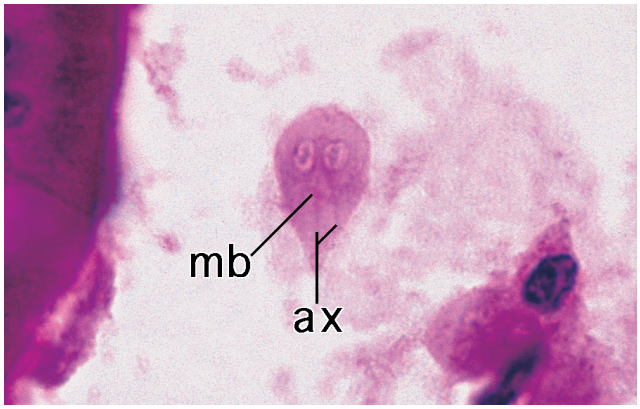

Figure 6.2
Higher magnification of *Giardia intestinalis* trophozoite in lumen of duodenum from same specimen as in Figure 6.1. Note paired nuclei with large karyosomes, and faintly stained median body (mb) and axonemes (ax). x 1330

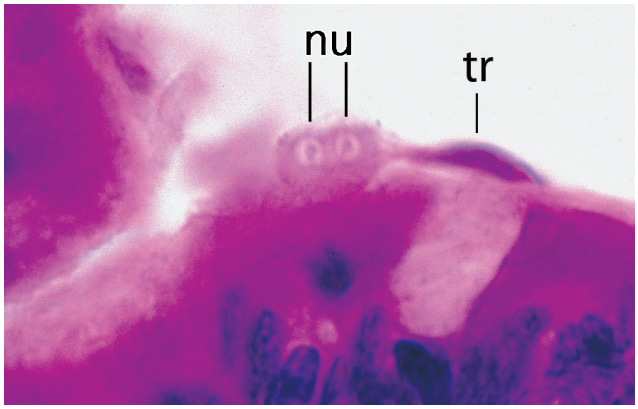

Figure 6.3
Two *Giardia intestinalis* trophozoites attached to surface of duodenal epithelium. Note paired nuclei (nu) of trophozoite at left and lateral view of a trophozoite (tr) at right. x1600

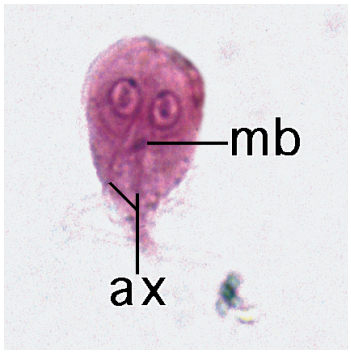

Figure 6.4
Giardia intestinalis trophozoite in lumen of duodenum. Note pear shape, 2 nuclei with karyosomes, and faintly stained median body (mb) and axonemes (ax). Movat x1800

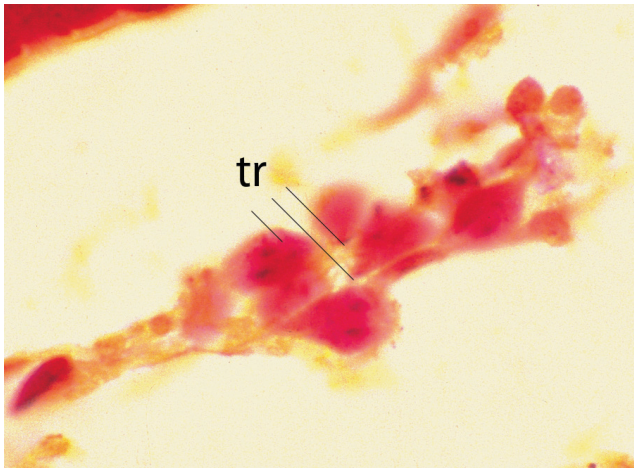

Figure 6.5
Giardia intestinalis trophozoites (tr) in lumen of small intestine depicting paired nuclei. B&H x1400

children under 3 years can reach 50%. In the United States, although underreporting is likely, approximately 19,000 cases were reported yearly between 2006 and 2008.[1,2]

Humans are infected by ingesting water or food contaminated with *Giardia* cysts or by fecal-oral transmission. Waterborne outbreaks of giardiasis have been linked to unfiltered water from shallow wells, persistent contamination of communal drinking water sources, and ingestion of water from recreational sources such as swimming pools. In the United States, most cases of giardiasis are reported in late summer and early fall, the peak seasons for recreational water sports. Foodborne outbreaks are well-documented, as is person-to-person transmission among homosexual men and among children and staff in day care facilities. The cyst wall of *G. intestinalis* is resistant to chlorine. Before water treatment standards in the United States became more stringent, waterborne transmission of *G. intestinalis* accounted for an estimated 25% of reported cases of giardiasis. In 2002 giardiasis became a nationally notifiable disease in the United States. Enactment of the Surface Water Treatment Rule and the Ground Water Rule by the EPA has decreased the number of ground water associated giardiasis outbreaks.[1]

The importance of giardiasis as a zoonotic disease is controversial, although there has been documented evidence of the zoonotic transmission of *Giardia* sp. Many studies on genotyping of various zoonotic *Giardia* sp have shown that the genotypes found in the zoonotic species (C through G) have not been found in humans. Although there has been documented evidence of *Giardia* sp transmission from animals to humans and humans to animals, zoonotic transmission is generally considered to be of minor consequence .[3-6]

Infectious Agent

Morphologic Description

Giardia intestinalis exists in 2 stages: trophozoite and cyst. Trophozoites, the only stage seen in biopsy and autopsy specimens, are pear-shaped and bilaterally symmetrical. Trophozoites range in size from 10 to 20 µm long, 5 to 15

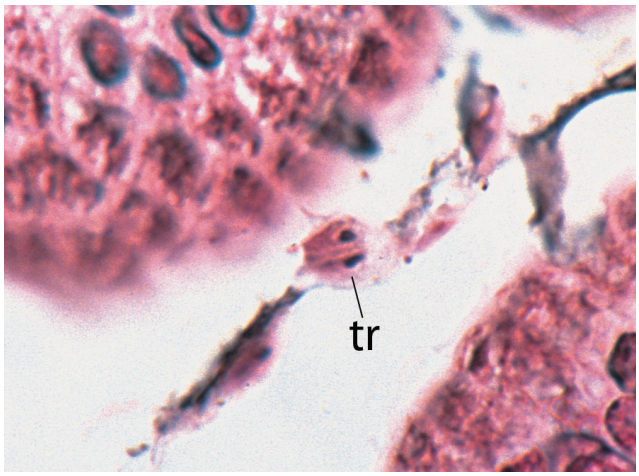

Figure 6.6
Giardia intestinalis trophozoite (tr) in lumen of small intestine showing paired nuclei and 2 axonemes. Wilder's reticulum x1390

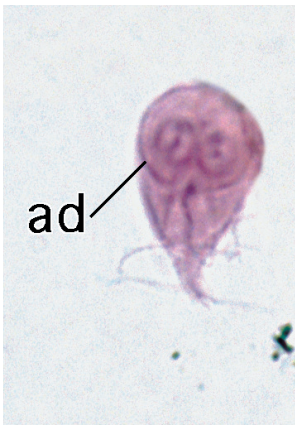

Figure 6.7
Same *Giardia intestinalis* trophozoite in lumen of duodenum shown in Figure 6.4, but at a different plane. Note large ventral adhesion disk (ad). Paired nuclei are visible at this level, though slightly out of focus. Movat x1500.

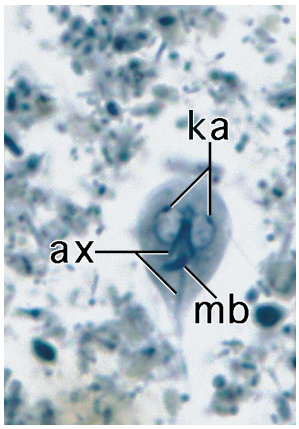

Figure 6.8
Giardia intestinalis trophozoite in smear of stool specimen. Paired nuclei with karyosomes (ka), median body (mb), and axonemes (ax) are clearly visible. Iron hematoxylin x1630

µm wide, and 2 to 4 µm thick (Figs 6.1 to 6.3). There are 2 nearly identical ovoid nuclei, each having a large central karyosome (Figs 6.2 & 6.4 to 6.6). A large adhesion disk is conspicuous on the anterior ventral surface (Fig 6.7). Pairs of axonemes give rise to 8 long flagella that stain poorly and are rarely observed. Trophozoites typically contain 2 curved rods, called median bodies, that lie posterior to the nuclei near the center of the cell (Fig 6.8). Trophozoites reproduce by longitudinal binary fission and can be cultured from duodenal aspirates (Fig 6.9).

The cyst stage of *G. intestinalis* is usually recovered from stool specimens. Cysts are ovoid to ellipsoid and measure 8 to 12 µm by 5 to 10 µm (Figs 6.10 & 6.11). The cyst wall is 0.3 to 0.5 µm thick. Mature cysts contain 4 nuclei, usually located at one end of the cyst, with each typically containing a spherical karyosome (Figs 6.10 & 6.12). Cysts also have median bodies, an adhesion disk, and retractile flagella in axonemes that appear as fibrils (Fig 6.13).

Clinical Features and Pathogenesis

As few as 10 to 25 cysts can cause infection in humans.[7] The incubation period can be as long as 10 weeks, but is usually 1 to 2 weeks. Gastric acid and pancreatic enzymes induce excystation of trophozoites. These trophozoites colonize the small intestine, especially the duodenum, by attaching to enterocytes, possibly by specific receptor ligands.[8]

The mechanism by which *G. intestinalis* causes gastrointestinal dysfunction is not completely understood. The number of trophozoites adhering to the gut mucosa directly effects the proper absorptive and enzymatic functions of the intestine. Immune-mediated mechanisms,[9] competition for essential nutrients within the intestinal lumen, bacterial overgrowth, and the formation of a physical barrier to absorption are proposed mechanisms. There may be a significant decrease of brush border enzymes and malabsorption of fat, vitamins A and B12, disaccharides, and protein.[10]

Clinical presentation of giardiasis ranges from asymptomatic infections to fulminant diarrhea, malabsorption and severe malnutrition. In asymptomatic infections only the passage of cysts in stool indicates the presence of parasites. Symptomatic giardiasis can be acute or chronic. The acute stage of infection is marked by the sudden onset of explosive, watery, malodorous diarrhea. Epigastric cramps are accompanied by bloating, flatulence, sulfuric belching,

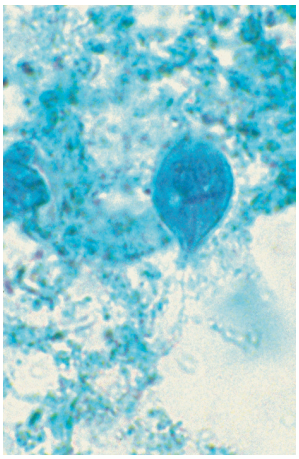

Figure 6.9
Giardia intestinalis trophozoite in smear from culture. Trichrome x1450

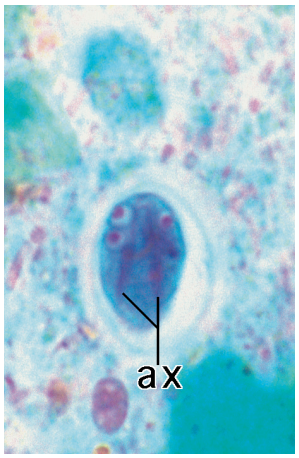

Figure 6.10
Giardia intestinalis cyst in smear of stool specimen. Axonemes (ax) and 3 of 4 nuclei are visible at this level. Median bodies are barely discernible. Trichrome x2025

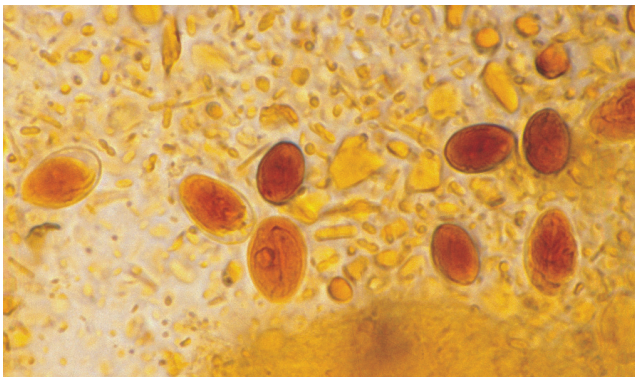

Figure 6.11
Several *Giardia intestinalis* cysts in wet mount of stool specimen. Iodine x715

malaise, weight loss, anorexia, and nausea. Continuous or intermittent diarrhea is the cardinal clinical complaint. Stools may be fatty but typically do not contain mucus, blood, or pus. The acute stage lasts from a few days to 2 or 3 months. White blood cell counts are normal and there is no eosinophilia. Persistent symptoms may mimic hiatal hernia, ulcer, or gallbladder disease.[11] Many patients with recurrent diarrhea after treatment are actually experiencing temporary lactose intolerance, not a relapse of infection.[10]

Humoral, cellular, and mucosal responses play a role in immunity to giardiasis.[12] The intestinal IgA response to acute infection is critical, as are the proliferative responses of the mesenteric lymph nodes and Peyer's patches. Nitric oxide synthesized by the intestinal epithelial cells is antiparasitic.[13]

Although asymptomatic infections are more often seen in children, chronic childhood giardiasis can cause malabsorption, weight loss, retarded growth, and zinc deficiency.[14] Persistent diarrhea can produce hypokalemia, especially in elderly hospitalized patients.[15] Rare extraintestinal manifestations such as hepatobiliary disease, and allergic reactions including urticaria, angioedema, and arthropathy have been reported.[16] Patients with AIDS may develop a giardiasis refractory to treatment if they are severely immunosuppressed.[17]

Pathologic Features

Most patients with giardiasis have normal duodenal mucosa (Fig 6.14). It is important to look for *G. intestinalis* in endoscopic biopsies that show normal small intestinal mucosa. Organisms do not invade tissue but are located in the lumen or attached to the epithelial surface of the villi. Laterally oriented organisms, especially when scant, may be easily overlooked (Fig 6.15). Reported cytologic and architectural changes include epithelial cell damage, loss of the brush border, villous atrophy, crypt hyperplasia, increased goblet cells, intraepithelial lymphocytes, increased inflammatory cells within the lamina propria, nodular lymphoid

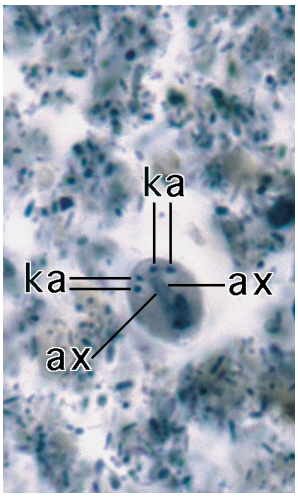

Figure 6.12
Giardia intestinalis cyst in smear of stool specimen. Axonemes (ax) and 4 karyosomes (ka) are visible at this level. Iron hematoxylin x1405

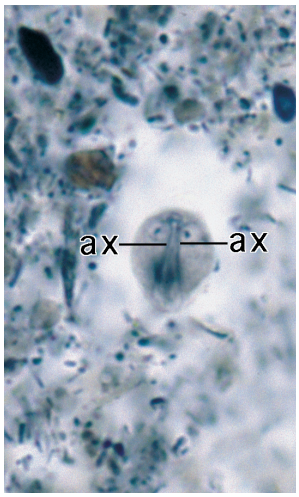

Figure 6.13
Giardia intestinalis cyst in smear of stool specimen. Axonemes (ax), 2 nuclei with karyosomes, and both median bodies are seen at this level. Iron hematoxylin x1575

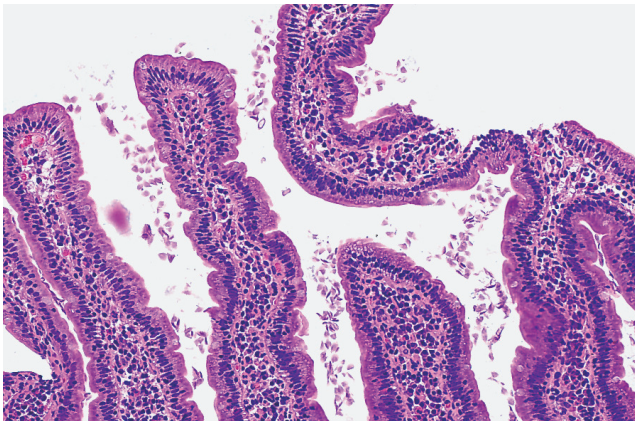

Figure 6.14
Many *Giardia intestinalis* trophozoites in lumen of duodenum. Note normal mucosa. x115

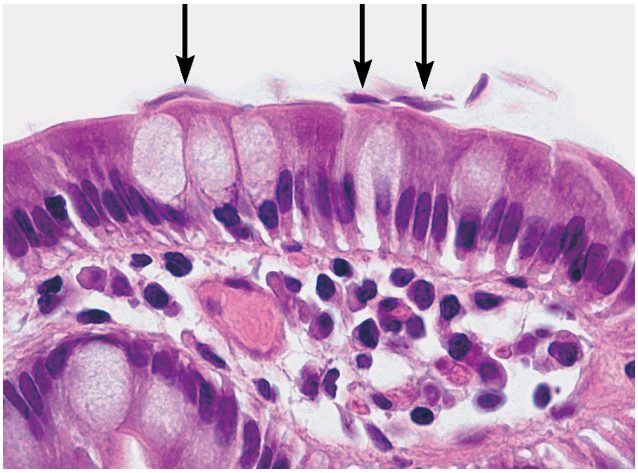

Figure 6.15
Laterally oriented *Giardia intestinalis* trophozoites (arrows) on surface of duodenal mucosa. x 590

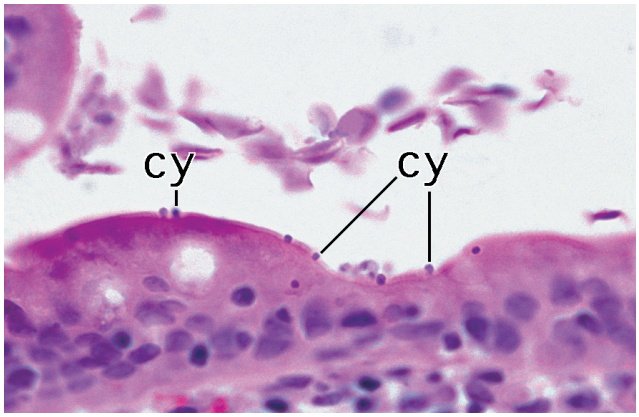

Figure 6.16
Biopsy specimen of duodenum from 46-year-old patient with chronic diarrhea and both giardiasis and cryptosporidiosis. *Giardia intestinalis* trophozoites are in the lumen, whereas *Cryptosporidium parvum* cysts (cy) are attahed to the epithelium. x605

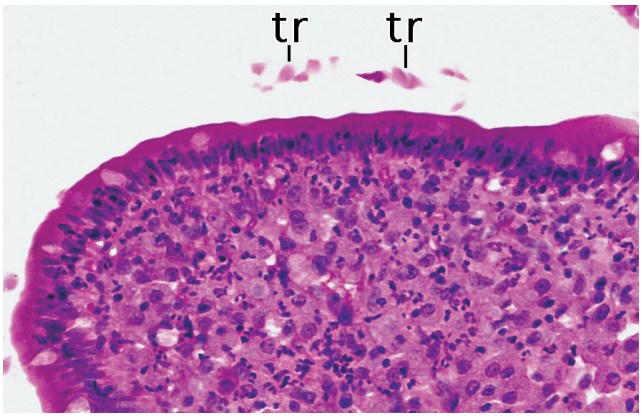

Figure 6.17
Biopsy specimen of duodenum from patient with both giardiasis and Whipple's disease. Lumen contains *Giardia intestinalis* trophozoites (tr), but neutrophils and histiocytes in lamina propria are attributed to Whipple's disease. x260

hyperplasia, acute inflammation, and crypt abscesses.[18-20] Some of these features may be seen in small intestinal biopsies from patients with giardiasis and other concomitant diseases such as cryptosporidiosis (Fig 6.16), Whipple's disease (Fig 6.17), or hypogammaglobulinemia (Figs 6.18 and 6.19). The histologic features of giardiasis are similar in immunocompromised and immunocompetent patients. Gastric biopsies from patients with chronic atrophic gastritis with intestinal metaplasia may reveal giardiasis[21], and trophozoites may rarely colonize the biliary tree and gallbladder.

Diagnosis

Definitive diagnosis is made by demonstrating *G. intestinalis* in stool specimens, duodenal contents, or intestinal biopsy specimens. In most patients, microscopic examination of 3 consecutive stool specimens collected 2 days apart is sufficient to establish or eliminate a diagnosis. Stool specimens usually contain cysts only, but trophozoites may be found in stools from patients with severe diarrhea (Fig 6.8). The parasite can be seen on wet mounts stained with trichrome (Fig. 6.10), iodine (Fig 6.11), or iron hematoxylin (Figs 6.12 & 6.13). In some patients, when stool examination is negative, motile trophozoites may be observed in Giemsa-stained smears of duodenal fluid, collected by the string test or aspiration.

Endoscopic biopsy can reveal other upper intestinal parasites (*Cryptosporidium* (Fig 6.16), *Cyclospora*, or microsporidia) and detect other causes of malabsorptive diarrhea such as celiac disease. *Giardia intestinalis* trophozoites, most numerous in the lumen of the duodenum and upper jejunum, are usually adequately demonstrated in histologic preparations of biopsy specimens stained with hematoxylin and eosin (Figs 6.1, 6.2, & 6.16). Special stains such as

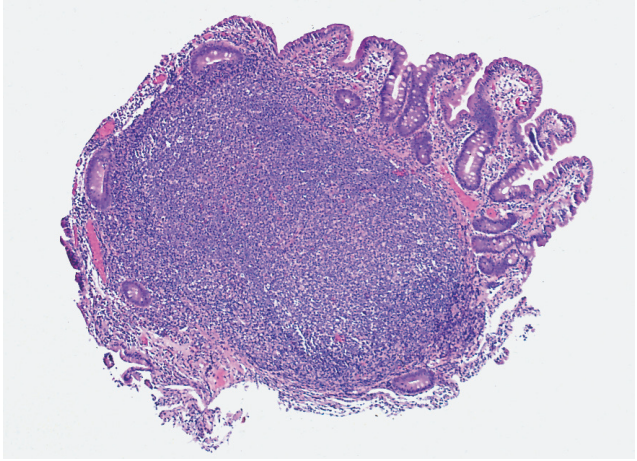

Figure 6.18
Lymphoid hyperplasia in duodenum is prominent in patient with hypogammaglobulinemia and associated giardiasis. x40

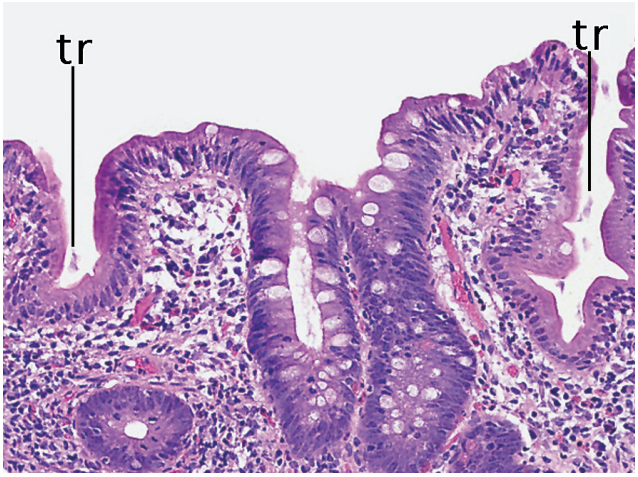

Figure 6.19
Higher magnification of duodenum depicted in Figure 6.18. Note several *Giardia intestinalis* trophozoites (tr) in lumen. x160

Movat, Brown and Hopps (Fig 6.5), and Wilder's reticulum (Fig 6.6) may accentuate the paired nuclei. Trophozoites may be demonstrated cytologically by a touch preparation of fresh biopsy specimen stained with Giemsa.

Numerous commercial antigen detection assays are available commercially and are reasonably reliable when compared with stool examination.[22] Immunochromatographic dipstick tests (ICT), direct fluorescent antibody (DFA) assays, and enzyme immunoassays (EIA) are available. Molecular techniques are sensitive and specific but not widely available.

Treatment and Prevention

Giardiasis is most commonly treated with metronidazole, tinidazole or nitazoxanide. Paromomycin may be used to treat pregnant women as it is poorly absorbed. Alternative medications are albendazole, paromomycin, furazolidone, and quinacrine. Extended treatment may be necessary for immunocompromised patients. A combination of metronidazole and quinacrine has been used in refractory cases.[23]

The key to the prevention of giardiasis transmission lies in preventing fecal contamination of food and water, and preventing direct transmission. Drinking untreated water should be avoided. Control measures include removing *Giardia* cysts from water by filtration, flocculation, and sedimentation. Chlorination alone is insufficient. Avoid eating food prepared with untreated water. Adequate personal hygiene, including hand washing, can prevent fecal-oral transmission. Keeping young children with diarrhea away from day care type settings and public recreational water facilities can help prevent waterborne transmission. The proper use of protective barriers during anal-oral sex will prevent sexual transmission of *Giardia* cysts.

References

1. Yoder JS, Harral C, Beach MJ. Giardiasis Surveillance—United States, 2006-2008. *MMWR CDC Surveill Summ.* 2010;59(SS06):15-25.
2.. Furness BW, Beach MJ, Roberts JM. Giardiasis surveillance—United States, 1992-1997. *MMWR CDC Surveill Summ.* 2000;49:113
3. Palmer CS, Traub RJ, Robertson ID, Devlin G, Rees R, Thompson RC. Determining the zoonotic significance of *Giardia* and *Cryptosporidium* in Australian dogs and cats. *Vet Parasitol.* 2008;154;142-147.
4. Isaac-Renton JL, Cordeiro C, Sarafis K, Shahriari H. Characterization of *Giardia duodenalis* isolates from a waterborne outbreak. *J Infect Dis.* 1993; 167;431-440.
5. Thompson RC, Palmer CS, O'Handley R. The public health and clinical significance of *Giardia* and *Cryptosporidium* in domestic animals. *Vet J.* 2008; 177:18-25.
6. Traub RJ, Monis PT, Robertson I, Irwin P, Mencke N, Thompson RC. Epidemiological and molecular evidence supports the zoonotic transmission of *Giardia* among humans and dogs living in the same community. *Parasitology* . 2004;128:253-262.
7. Rendtorff RC, Holt CJ. The experimental transmission of human intestinal protozoan parasites. IV Attempts to transmit *Endamoeba coli* and *Giardia lamblia* cysts by water. *Am J Hyg.* 1954;60:327-338.
8. Weiland ME, Palm JE, Griffiths WJ, McCaffery JM, Svard SG. Characterisation of alpha-1 giardin: an immunodominant *Giardia lamblia* annexin with glycosaminoglycan-binding activity. *Int J Parasitol.* 2003;33:1341-1351.
9. Faubert G. Immune response to *Giardia duodenalis*. *Clin Microbiol Rev.* 2000;13:35-54.
10. Hill DR. Giardiasis. Issues in diagnosis and management. *Infect Dis Clin North Am.* 1993;7:503-525.
11. Wolfe MS. Giardiasis. *Clin Microbiol Rev.* 1992;5:93-100.
12. Roxstrom-Lindquist K, Palm D, Reiner D, Ringqvist E, Svard SG. *Giardia* immunity: an update. *Trends Parasitol.* 2006;22:26-31.
13. Eckmann L, Laurent F, Langford TD, et al. Nitric oxide production by human intestinal epithelial cells and competition for arginine as potential determinants of host defense against the lumen-dwelling pathogen *Giardia lamblia*. *J Immunol.* 2000;164:1478-1487.
14. Jendryczko A, Sodowska H, Drozdz M. Zinc deficiency in children infected with *Giardia lamblia* [in Polish]. *Wiad Lek.* 1993;46:32-35.
15. Addiss DG, Lengerich EJ. Hypokalemic myopathy induced by *Giardia lamblia* [letter]. *N Engl J Med.* 1994;330:66-67.
16. McKnight JT, Tietze PE. Dermatologic manifestations of giardiasis. *J Am Board Fam Pract.* 1992;5:425-428.
17. Nash TE, Ohi CA, Thomas E, Subramania G, Keiser P, Moore TA. Treatment of patients with refractory Giardiasis. *CID.* 2001;33:22-28.
18. Oberhuber G, Kastner N, Stolte M. Giardiasis: a histologic analysis of 567 cases. *Scand J Gastroenterol.* 1997;32:48-51.
19. Oberhuber G, Stolte M. Giardiasis: analysis of histological changes in biopsy specimens of 80 patients. *J Clin Pathol.* 1990;43:641-643.
20. Ward H, Jalan KN, Maitra TK, Agarwal SK, Mahalanabis D. Small intestinal nodular lymphoid hyperplasia in patients with giardiasis and normal serum immunoglobulins. *Gut.* 1983;24:120-126.
21. Doglioni C, De Boni M, Cielo R, et al. Gastric giardiasis. *J Clin Pathol.* 1992;45:964-967.
22. Weitzel T, Dittrich S, Mohl I, Adusu E, Jelinek T. Evaluation of seven commercial antigen detection tests for *Giardia* and *Cryptosporidium* in stool samples. *Clin Microbiol Infect.* 2006;12:656-659.
23. Drugs for Parasitic Infections. Treatment Guidelines from *The Medical Letter*. 2010;Vol 8(Suppl).